Molecular and Functional Diversity of Histamine Receptor Subtypes

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The early history of histamine is largely associated with allergy. The major actions of histamine were described at the beginning of this century by Sir Henry Dale and his colleagues after its isolation from ergot extracts. Namely, its potent contractile effects on smooth muscles and the capillary dilation it induces, which mimic some initial manifestations of the anaphylactic shock, were identified by these scientists. They also detected the presence of the amine in many tissues, but it was another British scientist, Feldberg, who clearly demonstrated that histamine was released from the lung during the anaphylactic response and that it induced a marked bronchoconstriction.

The idea that histamine exerts its various biological effects via interaction with several distinct receptor subtypes progressively arose mainly with the design of subtype-selective antagonists. It was first realized that the "antihistamines" (now termed H_1-receptor antagonists), the first of which were designed by Bovet and Staub,[1] did not block uniformly all actions of histamine, leaving, for instance, gastric secretion unaffected. On this basis as well as on the differential action of agonists, Ash and Schild[2] clearly postulated the existence of a second receptor subtype. The existence of the H_2 receptor was definitively established with the design of burimamide, a selective (non-H_1) antagonist, as well as of several relatively selective agonists.[3]

Arrang *et al.*[4] proposed the existence of the third receptor subtype, an autoreceptor controlling the synthesis and release of histamine in cerebral neurons. Four years later, the existence of the H_3 receptor was definitively established with the design of highly potent and selective agonists and antagonists.[5]

The fields of histamine receptor pharmacology and biochemistry were recently reviewed in an extensive manner.[6–8] However, the very recent cloning of the genes encoding the histamine H_1- and H_2-receptor subtypes has notably enlarged our knowledge of these receptors. Although the histamine H_3 receptor has not yet been cloned, all three seem to belong to the superfamily of receptors with seven transmembrane domains and coupled to guanylnucleotide-sensitive G-proteins (TABLE 1).

THE HISTAMINE H_1 RECEPTOR

The H_1-receptor pharmacology was initially defined in functional assays such as smooth muscle contraction, with the design of potent antagonists, the so-called

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antihistamines, most of which are known to interfere with central histaminergic transmissions and display prominent sedative properties. Biochemical and localization studies of the H_1 receptor were made feasible with the design of reversible and irreversible radiolabeled probes such as [^{3}H]mepyramine, [^{125}I]iodobolpyramine, and [^{125}I]iodoazidophenpyramine (reviewed in refs. 9–11).

Initial biochemical studies indicated that the cerebral guinea pig H_1 receptor was a glycoprotein of apparent molecular mass of 56 kDa with critical disulfide bonds and that agonist binding was regulated by guanyl nucleotides, implying that the receptor

TABLE 1. Properties of Three Histamine Receptor Subtypes

Property	H_1	H_2	H_3
Coding sequence	491 a.a. (bovine) 488 a.a. (guinea pig) 486 a.a. (rat) 487 a.a. (human)	358 a.a. (rat) 359 a.a (dog, human)	?
Chromosome localization	Chromosome 3	?	?
Highest brain densities	Thalamus Cerebellum Hippocampus	Striatum Cerebral cortex Amydgala	Striatum Frontal cortex Substantia nigra
Autoreceptor	No	No	Yes
Affinity for histamine	Micromolar	Micromolar	Nanomolar
Characteristic agonists	2(m. chlorophenyl) histamine	Impromidine Sopromidine	(R)α-methylhistamine Imetit
Characteristic antagonists	Mepyramine (pyrilamine)	Cimetidine	Thioperamide
Radioligands	[^{3}H]Mepyramine [^{125}I]Iodobolpyramine	[^{3}H]Tiotidine [^{125}I]Iodoamino-potentidine	[^{3}H](R)α-methylhistamine [^{125}I]Iodophenpropit [^{125}I]Iodoproxyfan
Second messengers	Inositol phosphates (+) Arachidonic acid (+) cAMP (potentiation)	cAMP (+) Arachidonic acid (−) Ca^{2+} (+)	Inositol phosphates (−)

a.a.: Amino acid residue.

belongs to the superfamily of receptors coupled to G-proteins. In addition, various intracellular responses were found to be associated with H_1-receptor stimulation, for example, inositol phosphate release, increase in Ca^{2+} fluxes, cyclic AMP and cyclic GMP accumulation in whole cells, arachidonic acid release.[6,12] It was not known, however, whether such a variety of responses corresponds to a single receptor or to distinct isoreceptors. Indeed several photoaffinity-labeled proteins of slightly different masses, but similar H_1 pharmacology, were detected in some tissues.[10]

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In spite of preliminary attempts using affinity columns with a mepyramine derivative, the H_1 receptor was never purified to homogeneity. Nevertheless, the deduced amino acid sequence of a bovine H_1 receptor was recently disclosed after expression cloning of a corresponding cDNA. The latter was based upon the detection of a Ca^{2+}-dependent Cl^- influx into microinjected *Xenopus* oocytes. Following the transient expression of the cloned cDNA into COS-7 cells, the identity of the protein as an H_1 receptor was confirmed by binding studies.[13] More recently, by using the cloned bovine cDNA as a probe, the gene encoding the H_1 receptor was isolated in rats,[14] guinea pigs,[15,16] and humans.[17]

We recently cloned a guinea-pig cDNA encoding an H_1 receptor in order to identify the signaling systems of the H_1 receptor in a well-studied animal species, as well as to assess the possible existence of isoreceptors.[16] It encodes a glycoprotein of 488 amino acids (FIG. 1) with a calculated M_r of 56 kDa, in good agreement with the apparent size of the photoaffinity-labeled receptor from guinea-pig brain or heart, as determined by SDS/PAGE analysis.[18,19] Northern blot analysis of a variety of guinea-pig peripheral or cerebral tissues identified, in most cases, a single transcript of 3.3 kb. However, in some tissues—for example, ileum or lung—a second transcript of 3.7 kb was generated, possibly by the use of distinct promoter or polyadenylation sites or corresponding to a transcript from a distinct gene.[15,16]

In situ hybridization studies showed a highly contrasted expression of the H_1 receptor gene transcript in guinea-pig brain.[16] When compared with the autoradiographic localization of the corresponding receptor protein,[20] consistent as well as complementary information was provided. For instance, the mRNAs were found in high levels in cerebellar Purkinje cells and hippocampal pyramidal cells, whereas dense [^{125}I]iodobolpyramine binding sites are found in the molecular layers of both areas. This presumably reflects the synthesis of the receptor in perikarya and its final insertion in membranes of the abundant dendritic trees of both cell types.

Transfection with the guinea-pig gene followed by stable expression of H_1 receptors by a CHO cell line allowed the characterization of multiple signaling pathways.[21] In each case the involvement of a G_i/G_o protein with pertussis toxin (PTX), the influence of extracellular Ca^{2+} and of protein kinase C (PKC) activation by phorbol 12-myristate 13-acetate (PMA) were assessed.

Histamine induced in a PTX- and PMA-insensitive manner a biphasic increase in intracellular Ca^{2+} level of which only the second, sustained phase was dependent on the extracellular Ca^{2+} level. In addition, histamine also caused a threefold elevation of inositol phosphate production, which was PTX-insensitive but slightly inhibited by PMA and reduced by 75% in the absence of extracellular Ca^{2+}.

Histamine also caused a massive release of arachidonic acid (AA), occurring in a Ca^{2+}- and PMA-sensitive manner, probably through the activation of a cytosolic phospholipase A_2, which partly involves coupling to a PTX-sensitive G-protein. In comparison, in HeLa cells endowed with a native H_1 receptor, the histamine-induced arachidonic acid release was also Ca^{2+}- and PMA-sensitive, but totally PTX-insensitive.

Finally, in the same CHO(H_1) cell line, histamine in very low concentrations potentiated the cyclic AMP accumulation induced by forskolin. This response appeared to be insensitive to PTX, extracellular calcium, and PMA.

These various observations show that stimulation of a single receptor subtype, the guinea-pig H_1 receptor, can trigger four major intracellular signals, presumably through coupling to several G-proteins, which are variously modulated by extracellular Ca^{2+} and PKC activation.

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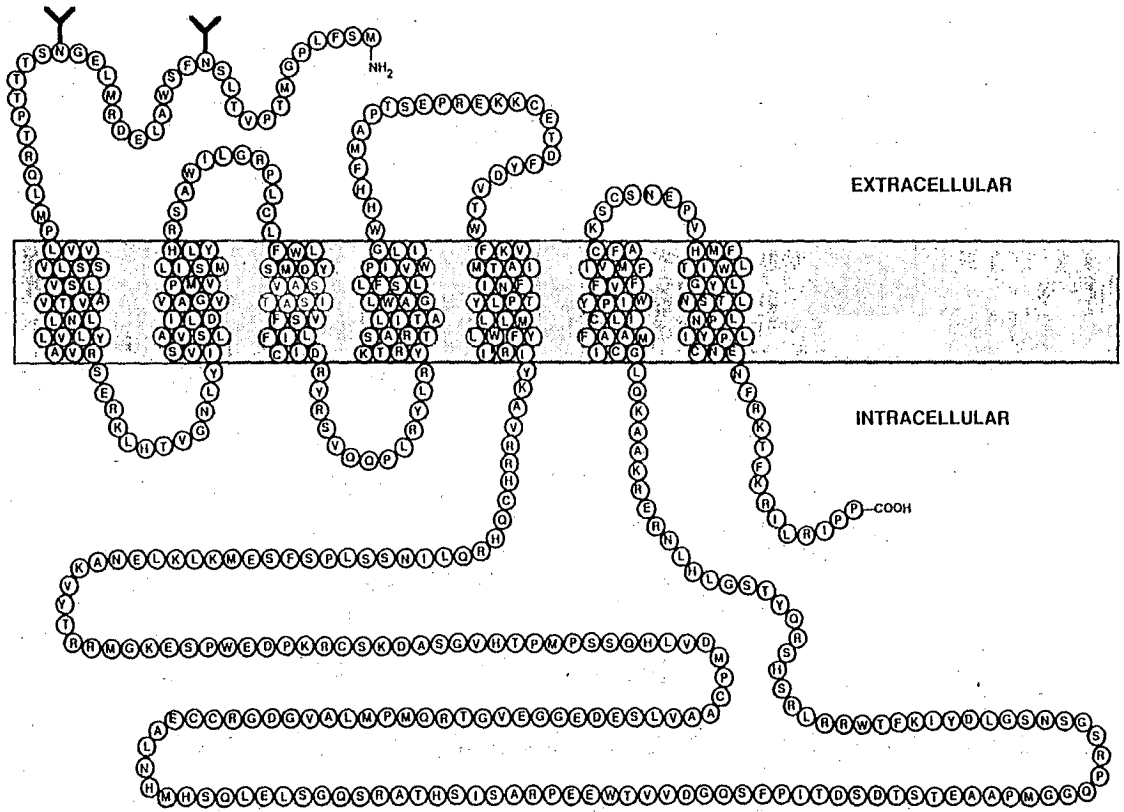

FIGURE 1. Amino acid sequence of the guinea-pig histamine H_1 receptor. Y indicates the presence of glycosylation sites.

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THE HISTAMINE H_2 RECEPTOR

Until recently, the information on H_2 receptors was mainly derived from the physiological and biochemical responses they mediate, and molecular properties of the H_2 receptor have remained largely unknown for a long time. For instance, only recently the reversible labeling of the H_2 receptor was achieved using [^{3}H]tiotidine[22] or, more reliably, [^{125}I]iodoaminopotentidine.[23] Irreversible labeling, achieved with a photoaffinity probe, followed by SDS-PAGE, led to the identification of H_2 receptor peptides from the guinea-pig brain.[23]

By screening cDNA or genomic libraries with homologous probes, the gene encoding the H_2 receptor was first identified in dogs[24] and, subsequently, in rats[25] and humans.[26] Comparison of these proteins shows that they display a high degree of homology, that is, 82% between the rat and dog receptor (FIG. 2), whereas the degree of homology between the H_1 and H_2 receptors is limited. The H_2 receptor is organized like other receptors positively coupled to adenylyl cyclase; that is, it displays a short (30 amino acids) third intracellular loop and a long (71 amino acids) C-terminal cytoplasmic tail (FIG. 2).

Consistent with their histamine binding function, the H_2 receptors display in the third transmembrane helix (TM3) an aspartate residue (Asp^{98}) likely to bind the ammonium group of the endogenous ligand, because it is found in all other aminergic receptors. In the TM5, an aspartate and a threonine residue (Asp^{185} and Thr^{189} in the rat and Asp^{186} and Thr^{190} in the dog) seemed responsible for hydrogen bonding with the nitrogen atoms of the imidazole ring of histamine. This was partially confirmed by site-directed mutagenesis.[27]

A potential regulation of the rat H_2 receptor by phosphorylation is suggested by the presence of three consensus sites for protein kinase C.

Northern blot analysis of various tissues using a probe derived from the rat cDNA sequence revealed the presence of a single major transcript of 6.0 and 4.5 kb in rat and guinea pig, respectively.[25,28] The distribution of the mRNAs in these two species was consistent with the known distribution of the receptor as mainly established using the sensitive probe [^{125}I]iodoaminopotentidine.[23]

Transfected CHO cells were found to express a high level of rat H_2 receptors.[28] In these cells, histamine, in low concentration, induced an accumulation of cAMP, confirming the association of the H_2 receptor with adenylyl cyclase. In addition, in the same cells, histamine potently inhibited the release of arachidonic acid induced by stimulation of constitutive purinergic receptors or by application of a Ca^{2+} ionophore. This inhibition was independent of either cAMP or Ca^{2+} levels in the cells. The results indicate that a single H_2 receptor may be linked not only to adenylyl cyclase activation but also to reduction of phospholipase A_2 activity. Because H_1 receptors have been reported to stimulate arachidonic acid release, inhibition of this release, an unexpected signaling pathway for H_2 receptors, may account for the opposite physiological responses elicited in many tissues by activation of these two receptor subtypes.

In rat hepatoma-derived cells transfected with the canine H_2-receptor gene, histamine induced an increase in intracellular cAMP and Ca^{2+} concentrations, revealing in this system a positive coupling of the H_2 receptor to two signaling mechanisms.[29]

THE HISTAMINE H_3 RECEPTOR

The H_3 receptor was initially detected as an autoreceptor controlling histamine synthesis and release in brain.[4] It was thereafter shown to inhibit presynaptically the

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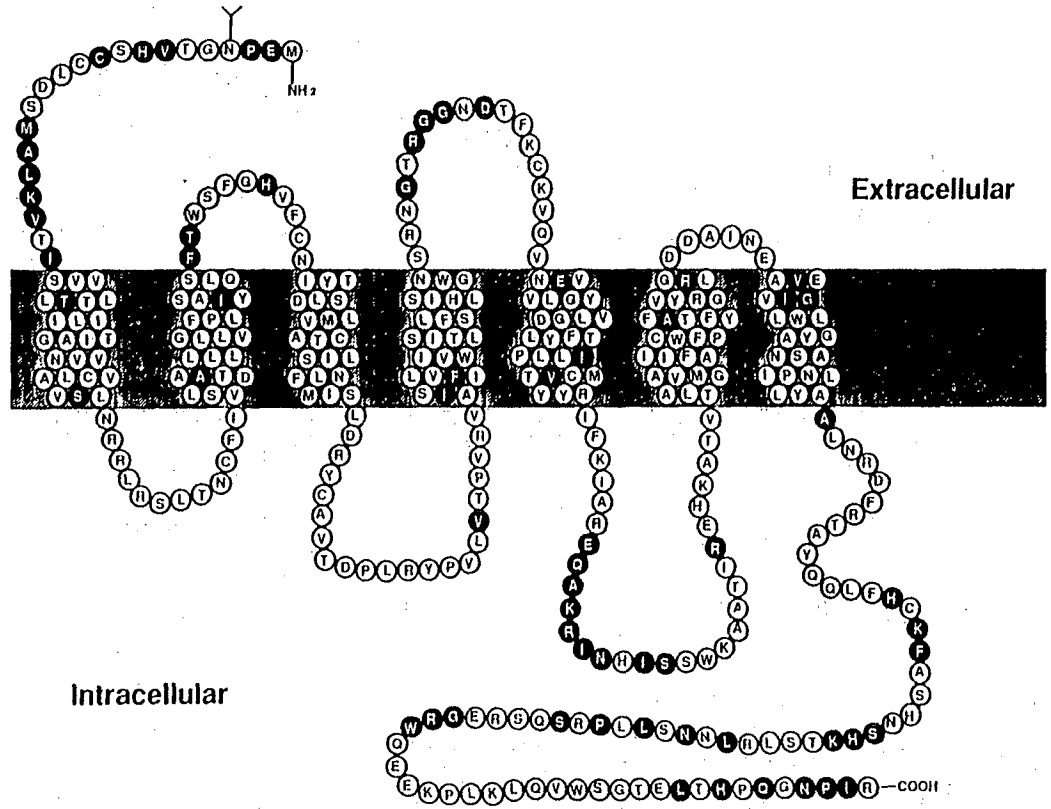

FIGURE 2. Amino acid sequence of the rat histamine H_2 receptor. The shaded amino acid residues are those that are not identical in dog and rat.

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release of other monoamines in brain and peripheral tissues as well as of neuropeptides from unmyelinated C-fibers (reviewed in refs. 7 and 30).

The molecular structure of the H_3 receptor remains to be established. Reversible labeling of this receptor was first achieved using a highly selective agonist [^{3}H](R)α-methylhistamine.[5] [^{3}H]N$^{\alpha}$-methylhistamine, a less selective agonist,[31] and, more recently, [^{125}I]iodoproxyfan, a selective antagonist,[32] were also proposed. It appears that the binding of [^{3}H](R)α-methylhistamine is regulated by guanyl nucleotides, strongly suggesting that the H_3 receptor, like the other histamine receptors, belongs to the superfamily of receptors coupled to G-proteins.[33] Constitutive H_3 receptors in a gastric cell line appear to be negatively coupled to phospholipase C.[34] In the vascular smooth muscle, H_3 receptors mediate voltage-dependent Ca^{2+}-channel stimulation via a pertussis-insensitive G-protein.[35]

During the last few years several potent and highly selective H_3 receptor agonists were designed.[36] Among them, (R)α-methylhistamine[5] and (R)α,(S)β-dimethylhistamine[36] display a high degree of stereoselectivity, imetit[37] being a nonchiral and very potent H_3-receptor agonist (TABLE 2).

TABLE 2. Potent and Selective H_3-Receptor Agonists

Compound	Relative Potency at Receptors		
	H_1	H_2	H_3
Histamine: Im-CH_2-CH_2-NH_2	100	100	100
(R)α-methylhistamine: Im-CH_2-$\underset{*}{CH}$(CH_3)-NH_2	0.5	1	1,500
(R)α,(S)β-dimethylhistamine: Im-$\underset{*}{CH}$(CH_3)-$\underset{*}{CH}$(CH_3)-NH_2	0.03	0.2	1,800
Imetit: Im-CH_2-CH_2-SC(NH_2)=NH	<0.1	0.6	6,200

By the use of these compounds as well as the prototypic H_3-receptor antagonist thioperamide,[5] several effects and physiological roles of histamine could be unraveled or confirmed.

In the brain, H_3-receptor ligands have largely confirmed the role played by histaminergic neurons in cortical activation and arousal mechanisms.[7,38] In the respiratory tract, H_3 receptors inhibit both acetylcholine release from the vagus nerve and the release of neuropeptides from sensory nerves.[39] In the digestive system, similar prejunctional H_3 receptors are involved in the regulation of gastrointestinal functions.[40] However, a direct stimulation of H_3 receptors on enterochromaffin-like cells in the effector organs has also been reported.[41,42] Both populations of H_3 receptors are likely to be involved in the regulation of gastric acid secretion.[40,43]

CONCLUSIONS

All three histamine receptor subtypes presently known were identified through the classical strategy based upon the design of a suitable bioassay and the synthesis of

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new chemical drugs. In the case of H_1 and H_2 receptors, this strategy has led not only to fundamental discoveries in the field of receptors, but, at the same time, to very useful drugs for treating life-threatening allergic and gastrointestinal disorders. A similar classical process involving a collaboration between pharmacologists and chemists led us to define the H_3 receptor. Although this remains to be firmly established, it can be anticipated that some of the H_3-receptor ligands will constitute novel drugs for the treatment of central or peripheral disorders in humans. The molecular biology approach has already allowed to complement, in greater detail, information about H_1 and H_2 receptors. It would be surprising if this cloning strategy, which has been so fruitful for the discovery of new isoforms or receptor subtypes, does not lead, as in other areas, to an expansion of the histamine receptor family during the coming years.

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